

HOW THE INTRODUCING OF RNA INTERFERENCE
CAN PROVENT THE DEVELPOMENT OF
NEURODEGENERATIVE DISEASES

BY
RACHEL JEWERS

PASS WITH MERIT

RESEARCH PAPER
BASED ON
PATHOLOGY LECTURES
AT VET-MEDLINK 2009

Abstract

The discovery of ribonucleic acid interference has sparked a wave of enthusiasm in the scientific community. Since the discovery of RNA interference scientists have used it to identify the molecular processes of different diseases. RNA interference has the potential to be used in a wide range of applications one of which is cancer therapies. The unique key to RNA interference as it does not have any of the side-effects normally attributed to the cure of these diseases. This is because it does not replicate the function of the degenerated part of the body but it prevents the degeneration in the first place. However there is always a problem with adding synthetic materials to the human body. Firstly we can not truly know how they will react until they are used and secondly they cause a mutation in the part of the human body they are implanted it causes that part to become inactive. We will also look at and try to weigh up the issues raised with this kind of revolutionary treatment and the possible ways it could be used to increase the length and quality of life.

Introduction

We will all suffer from hundreds of different illnesses at some point in our lives; the severity of which can range from the common cold to an illness that can threaten our lives. Some of these illnesses are easier for our immune system to fight off than others and a few we are all but defenseless against. As technology has developed scientists have slowly found ways to cure or prevent us from becoming ill mainly by the use of vaccinations. A vaccination is an injection of a killed microbe they are used in order to stimulate the immune system against the microbe, thereby preventing disease. Now we are faced with increasingly harder challenges, as these illnesses mutate to become immune to our defenses and the range of medicines we use against them. Some diseases that are becoming increasingly hard to treat with antibiotics are tuberculosis, gonorrhoea, pneumonia and septicemia. This is due to the increasing use of existing antibiotics in human and veterinary medicine and also in agriculture. A new way for us to fight these illnesses is RNA interference. RNA is a nucleic acid similar to DNA but contains ribose rather than deoxyribose. It forms on the template strand of DNA. RNA interference is believed to be able combat illnesses such as cancers, viruses and neurodegenerative disease which is becoming more and more frequent as life expectancy is increasing. This double strand RNA (dsRNA) is used as a viral defense in plants and invertebrates but not in humans. RNA interference was discovered in 1998 by two scientists, Andrew Fire and Craig Mello. Using nematode worms *Caenorhabditis elegans*, they investigated how gene expression is regulated. During their experiments they discovered that when they injected both "antisense" RNA and "sense" RNA together they joined to form double strand RNA (dsRNA). Long strands of this dsRNA trigger the interferon reaction, but short strands RNA (siRNA) trigger the interference response. This siRNA is most commonly between 19 and 23 nucleotides in length. Tests have revealed that the dsRNA seemed to silence the gene carrying the same code as the siRNA. The possible uses of this are vast not only for humans but for all mammals. This means it has both interest from the medical and veterinary professions. This would also allow us to use antibiotics less frequently which would slow the resistance of some bacteria. It could also be used to destroy cancers, neurodegenerative diseases, virus that alter the host's DNA, such as hepatitis B and parvovirus B19. In the case of cancer there were 12.2 million reported cases of which 7.5 million people died worldwide every year. With neurodegenerative diseases there are more than 20 million new cases every year.

Unfortunately as with every new scientific discovery there are several ethical issues that must be taken into account and if possible overcome before the therapy can become available to the public. This paper will focus on preventing the development of neurodegenerative diseases mainly Parkinson's diseases. It is not yet clear whether Parkinson's is a genetic disease or not. In some families there are some specific genetic

abnormalities that have been shown to lead to the disease but in the majority of cases the genetic abnormalities are not present. Parkinson's disease is caused by a lack of dopamine which is produced by neurons in the *substantia nigra*. The dopamine serves as a chemical messenger in the brain and allows communication between the *substantia nigra* and the *corpus striatum*. These two areas of the brain coordinate to allow smooth and balanced muscle movement. A lack of dopamine results in abnormal nerve functioning, causing a loss in the bodies' ability to control movement. The symptoms of Parkinson's disease usually begin slowly and develop gradually over time. Parkinson's effects people differently and the symptoms do not show in a particular order. There are three main symptoms for Parkinson's. Firstly, bradykinesia this is a slowness of movement and a loss of movement coordination. Secondly tremors this shaking will often occur first in the hands or arms and will become more noticeable with time. The final, symptom is a stiffness of the muscles which will make performing simple everyday tasks hard. This disease and others like it is becoming increasingly present as life expectancy is increasing.

Discussion

As medical science develops the life expectancy of our species increases. As it does so we are seeing more and more cases of neurodegenerative diseases such as Huntington's, Alzheimer's and Parkinson's. Nobody knows for sure whether a medical disorder is caused by genetics or not until it is specifically tested for. It is possible for relatives to experience the same neurodegenerative diseases and not to have inherited it. Neurodegenerative diseases normally occur due to a mutation in the DNA during division. Which results in a protein being synthesised with a different amino acid in the code which causes it shape to change due to the formation of different bonds. This strand of protein is synthesised in the ribosome and are coded for by messenger RNA (mRNA). mRNA is a type of RNA that reflects the exact nucleoside sequence of the genetically active DNA. mRNA carries the "message" of the DNA to the cytoplasm of the cells where protein is made in amino acid sequences specified by the mRNA. To form mRNA the double helix of DNA must uncoil and open out in doing so the hydrogen bonds between the template and coding strand break. Free RNA nucleotides then join to the complementary bases on the template strand of DNA. The arrangement of these bases will determine the chain of amino acids produced by the ribosomes. The change in the one of the base pairs will result in a different amino acid being produced. This could result in the protein folding in a different way that will cause it to be unable to perform the function it was designed for. The possibility of these mutations being destroyed by our bodies' immune system will at the very least slow the degeneration of the neurons which would allow movement control to be effective for longer. The most common treatment taken by people suffering from Parkinson's disease at present is a medicine that replaces dopamine. These medicines are a combination of levodopa, which is broken down in the formation of dopamine and another chemical which ensures the levodopa reaches the brain. Although this option is a long term treatment for people suffering from Parkinson's it does come with side-effects such as feeling sick, vomiting and sudden sleepiness in the short term. There are some long term problems such as unwanted movement of the face and limbs (dyskinesia). Many of these treatments can become less reliable over time. This will become more of a problem as life expectancy increases as people will rely on them for longer.

RNA Interference should not give any side-effects to the user as it will prevent the degeneration of the neurons in the *substantia nigra* rather than try to replace their function

once they are no longer working. The problem with using RNA interference to prevent the degeneration of cells in the human body is unlike a virus the degeneration of these cells in the body can happen in a number of ways. Some of these ways may not yet have been identified as a cause of the disease. Unlike degeneration a virus will only alter the DNA in one specific way which can easily be targeted. With degeneration the thing you must remember is that it is not one specific change in the DNA that you are looking for but instead you are trying to prevent a combination of any variety of changes that could or could not be responsible for the degeneration. Another obstacle that must be overcome is that, the degeneration can happen at any point so all the possible variations of the dsRNA must remain in all the possible effected cells for the duration of the individuals life. This make the job of preventing the degeneration that much harder. Bearing this in mind it would be much more effective if the specific dsRNA code to then be adapted in to the process of cell division so that the dsRNA code does not need to be re-administered. This would mean that every new cell in our body would then be able to pass it on to its daughter cell. The problem that could then occur is the one that we were trying to prevent in the first place, if the implanted dsRNA code was to mutate during the cell division it would then be ineffective against the virus or the specific mutation it was targeted at. This could result in the degeneration still occurring or in the case of a virus the host will become infected. In the worst case it could mutate into something that is vital to the cells survival and would destroy the normal function of the cell.

We can determine the problems that would be encountered with trying to add the synthetic dsRNA into the division process by looking at the work done by Chemists and synthetic biologists to see if they can expand the genetic code of proteins, with unnatural nucleotides that can be incorporated into DNA and RNA sequences and unnatural amino acids that can expand the chemical functionality of proteins. These amino acids can make the bonds inside the protein more stable which will allow them to be able to survive in harsher environments or add new chemical groups which will allow the protein to do new biochemical reactions. They are trying to do this by making a whole parallel genetic code in a living cell. This is designed to use evolution to direct a ribosome that can read four letter codons instead of the normal three. These problems range from being unable to accurately determine the way in which the synthetic dsRNA code will interact with the DNA already present in the cell. This could result in the normal function of the DNA being interrupted and vital protein chains no longer being synthesized. This would devastate the function of the cell causing unknown damage. This will also be majorly affected by the publics view on this, after all it is being developed to help the general public and many could view the change being made to the cells as scientists “playing God” this would be hard for people to come to grips with and only with the support of the public can this project have any change in helping people to survive viruses and prevent Nero degeneration.

If we somehow manage to add synthetic dsRNA codes into the nucleus of a cell in a way in which it can be incorporated into the cell without causing any changes to the existing DNA. Along with being able to incorporate it into the division process so that the original cell can pass a copy on to each of the daughter cells. Once all of this has been achieved a new problem will arise and this is one of space. There is only a finite amount of space inside the nucleus of a cell some of which is already occupied by the chromosomes. If we can find a way to introduce a dsRNA that can be used to prevent all the possible different viruses and the degeneration of a specific part of the body would it be possible of that specific dsRNA code to just be present in the required area. For instance the dsRNA code that prevent the degeneration of the neurons in the substantia nigra this is the only place it will need to be

present. For instance the dsRNA code that prevent the degeneration of the neurons in the substantia nigra this is the only place it will need to be present. This could be possible if we passed these dsRNA with the genetic coding of the parent to the offspring. These stem cells will then divide and specialize into the different tissues in the body. This would be the perfect way in which to ensure the specific dsRNA only went to the area that they where required eliminating the problem of over whelming the cell with too much genetic information. For some of the viruses that we are trying to arm ourselves against will only become a threat to us at certain points in our lives. However if the dsRNA code stays present in our cells for the whole of our lives this presents us with a much greater chance of a mutation that could become ineffective or that could cause damage to the natural function of the cell. This is where being able to introduce and take out the dsRNA codes when necessary will greatly increase the chance of success.

Another problem that must be over come before the wide spread use of RNA interference is that with adding the dsRNA into the cell is that once it has been introduced into the division process it will become just as susceptible to mutations as normal unaltered DNA. This could then cause a problem as we would make dsRNA that will code for the possible mutations in the primary dsRNA code all of this would result in a never ending circle unless we find a way in which we can produce the dsRNA so that it is resistant to mutations. The shorter the dsRNA code needed the less likely it will be to mutate.

The support of the general public is still the one necessity that will underpin the success of this project. One of the problems that must be over come is that the public seems to have a distrust of scientist with the view that they are trying to “play god” by altering thing that should ultimately not be ours to change. People could also see it as fundamentally changing who we are by adding thing to our DNA that are not naturally occurring. These issues must be weighed up against the fact that this new treatment could have the potential to cure all forms of cancer, every virus and prevent the degeneration of our cell as we age. For this project to take off the public must believe that the benefits out weigh the risks and that by adding the dsRNA codes into the body it does not change who we are. This is vital as ultimately the only way to be sure if the dsRNA code work with out side-effects is to put it in to practice and test is on people that are suffering from things such as cancer and hepatitis B. To be able to do this we need the backing of the public and people that believe in it enough to put them selves forward to trail the RNA interference.

Conclusion

RNA interference is a fantastic and exiting new way in which the medical and veterinary profession can strive to improve the quality and length of peoples and animals lives. The possibility that the dsRNA can be introduced to the body in a way that will allow them to naturally spread will illuminate the problem of maintaining the levels for the needed time. If it is possible for the dsRNA to be passed from the mother and farther to the child it is possible that when the stem cells specialize the dsRNA specialize to this will mean that getting the dsRNA to the relevant area of the body becomes easier. The only problem is trying to ensure that the dsRNA specialize to the desired area of the body where they can be used most effectively. The development of this treatment is very important as the potential number of life that it can save is vast and as life expectance increases these figures will rise. We already know the specific mutation or change to the hosts DNA caused by several viruses that occurs resulting in a cancerous growth or the infection of a virus. We now must synthesis a dsRNA code that can successfully be used to illuminate the undesired code to prevent it from using our cells to reproduce. Whilst doing this we must introduce the idea for this treatment to the general public to allow them time to come to grips with the issues and possible successes of this project as secrecy will ultimately only lead to suspicions and once this treatment has been properly developed we will need people that are suffering form these cancers and viruses to have enough support and belief in this treatment to be involved in the trial and hopefully long term use of this treatment.

Reference

1. [Expanding the Genetic Code](#)
Posted on: February 18, 2010 7:10 PM, by **Error! Hyperlink reference not valid.**
2. http://hcd2.bupa.co.uk/fact_sheets/html/parkinsons_disease.html
Parkinson's disease, Published by Bupa's health information team, April 2009
3. Definition of Ribonucleic acid (RNA)
<http://www.medterms.com/script/main/art.asp?articlekey=5366>
4. Definition of Vaccination
<http://www.medterms.com/script/main/art.asp?articlekey=5925>
5. <http://www.webmd.com/parkinsons-disease/parkinsons-causes>
Edited by Cynthia Dennison Haines, MD on June 01, 2005
6. THE EUAN MACDONALD CENTRE FOR MOTOR NEURONE DISEASE
RESEARCH THE UNIVERSITY OF EDINBURGH CAMPAIGN
<http://www.edinburghcampaign.com/Campaign/Default2.aspx?PageID=289>
7. http://nobelprize.org/nobel_prizes/medicine/laureates/2006/press.html
Andrew Fire and Craig Mello won the Nobel Prize in Physiology or Medicine for discovering RNAi mechanism
8. How Many People Die from Cancer Each Year
<http://www.ucan-behealthy.com/cancer/how-many-people-die-from-cancer-each-year/>
9. Pete Kennedy and Frank Sochacki, OCR biology AS, Heinemann publishing group
10. [RNA Interference in Biology and Medicine — Pharmacological Reviews](#) RNA interference in biology and medicine by Ollivier Milhavet, Devin S. Gary and Mark P. Mattson published in December 2003
11. [The genetic causes of Parkinson's disease](#)
12. [RNA Interference \(RNAi\) Resource](#)
13. Symptoms of Parkinson's disease
<http://www.nhs.uk/Conditions/Parkinsons-disease/Pages/Symptoms.aspx>
14. Lectures in Microbiology by Kenneth Todar PhD, 2009, University of Wisconsin-Madison Department of Bacteriology
<http://textbookofbacteriology.net/themicrobialworld/bactresanti.html>

15. [Gene Therapy \(2006\) 13, 464–477. doi:10.1038/sj.gt.3302694; published online 8 December 2005](#)